

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Kantamneni, Shobha
Art Unit : 1617
Applicants : Kivlighn et al.
Serial No. : 09/892,505
Filed : June 28, 2001
For : Treatment For Cardiovascular Disease

DECLARATION OF MATTHEW R WEIR, M.D.

I, Matt Weir, M.D., hereby declare and say as follows:

THAT, I am Professor and Director of the Division of Nephrology at the University of Maryland School of Medicine. I am a world expert in the field of hypertension and have published over 300 papers. I am well versed with the work of Dr Johnson, particularly as it relates to his work with uric acid.

THAT, I am aware of the level of skill of one ordinarily skilled in the art of cardiovascular disease and kidney disease, and in particular, mechanisms of hypertension, hereto; AND being thus duly qualified declare as follows:

1. I have read the Nakamoto European patent (Nakamoto Patent) cited by the Examiner in the subject application. The Nakamoto patent is directed to a new uricosuric compound; not to a xanthine oxidase inhibitor. Importantly, the Nakamoto patent makes a curious statement, which the U.S. Patent Office relies on for its allegation that Nakamoto discloses that compounds which reduce uric acid are effective in curing hypertension¹. Nakamoto reasons that if gout is associated with hypertension, then curing gout with its uricosuric compound will cure hypertension (page 7, last line). In fact, it has been known for over 40 years that uric acid is strongly associated with hypertension². Nevertheless, those skilled in the art of science and medicine are careful to not confuse something considered as an associative factor with something that is a causative factor. Nakamoto made the classic mistake of equating association with causation. As an example, let's assume that a study finds that drinking alcohol is associated with lung cancer. Those skilled in the art would not assume from this that

drinking alcohol causes lung cancer (rather the medical community would undoubtedly interpret this study to mean that many people who drink also smoke). The only way to determine whether abstaining from alcohol causes lung cancer or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study.


While the association of uric acid with hypertension has been known since our early work, this certainly did not prove that uric acid is a cause of hypertension. Indeed, the scientific community (as exemplified by guidelines published by the major societies on hypertension and cardiovascular disease) have not considered uric acid as having a causal role in hypertension. In this regard, Dr Johnson is the first to specifically investigate if uric acid might be a cause of hypertension and to provide direct evidence of such. As such, the Nakamoto reference is flawed from a medical/scientific perspective that even a person with little skill in the art would discount it outright, especially since Nakamoto provides zero supporting data or evidence that uric acid is a cause of hypertension. Consistent with this point, a literature search in the PubMed and patent search of the USPTO database using the authors' names (and U.S. Counterpart 4,883,821) identified no citations to their work.

2. Members of the famous Framingham Heart Study group, experts in the field of hypertension, declared in 1999 (note that the Nakamoto patent was issued in 1991) that uric acid does not play a causative role in hypertension³, such conclusion being supported by a comprehensive scientific study. Indeed, as of 2000, the scientific evidence, supported by actual research and data, lead those skilled in the art to believe that there is no reasonable expectation of successfully controlling hypertension by controlling a patient's uric acid levels. Said differently, the scientific, peer-reviewed literature taught away from controlling uric acid levels to control hypertension. Incidentally, in 2005, members of the Framingham Heart Study Group reversed their position and published an acknowledgement that serum uric acid plays a causative role in hypertension⁴, citing to Dr. Johnson's work⁵.

3. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information in belief are believed to

be true; and further that these statements were made with the knowledge that willful false statements in the like so made are punishable by fine or imprisonment, or both, under ' 1001 of title 18 of the U.S.C. and that such willful false statements made jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.


MATTHEW R. WOOD
[name]
12/31/07
Date

1. The Nakamoto patent states that its diuretic compound "is effective in curing gout by ameliorating and curing hyperuricemia. This disease often accompanies hypertension, arteriosclerosis and myocardial infarction because of characteristics of the disease.

Accordingly, the compound of the present invention is effective in curing or preventing hypertension, arteriosclerosis or myocardial infarction accompanied by hyperuricemia." (page 7, last line)

2. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. *N Engl J Med* 1966;275:457-64.

3. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7-13.

4. Sundstrom, J., L. Sullivan, R.B. D'Agostino, D. Levy, W.B. Kannel, and R.S. Vasan, *Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence*, Hypertension, 2005 45(1): p. 28-33)

5. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001;38:1101-6.